

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ





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Treatment of Angina

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Lecture 2:

INTENDED LEARNING OBJECTIVES (ILO)



- 1) Explain the role of Ca channel-blockers as antianginal drugs
- 2) Explain the uses adverse effects and drug interactions of Ca channel -blockers as antianginal drugs
- 3) Explain the role of beta -blockers as antianginal drugs
- 4) Identify anti-platelets drugs.
- 5) Identify other drugs used in anginal treatment.
- 6) Identify favorable and unfavorable anti-Anginal





2- Ca channel Blockers

Classification:

1- Non- Dihydropyridines heart inhibition > VD (Verapamil, diltiazem).



2- Dihydropyridines VD > heart inhibition

a- Long Acting: Amlodipine.

b- Intermediate Acting: Nifedipine, Nitrendipine, Felodipine & Isradipine.

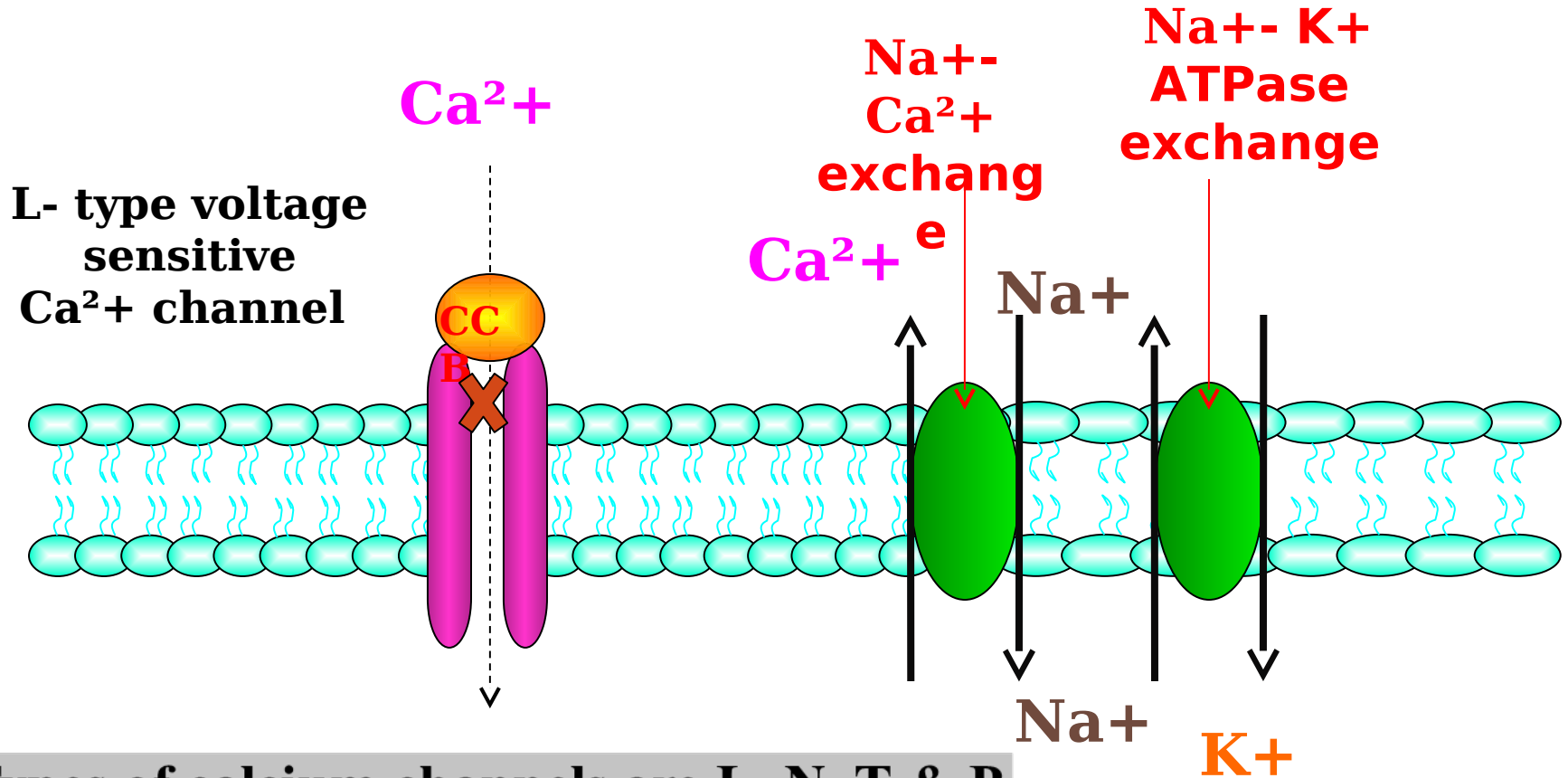
c- Short Acting: Nicardipine & Nimodipine.



Pharmacokinetics

	Verapamil	Diltiazem	Nifedipine
1- Oral Absorption :	Well	Well	Well
2- Oral bioavailability :	Low (20 %)	Moderate (40 %)	High (60 %)
3- First pass met. :	High	Moderate	Little
4- Binding to plasma proteins:	High (90 %)	High (80 %)	High (90 %)
5- Fate :	- Hepatic metabolism - Renal & biliary excretion	- Hepatic metabolism - Renal & biliary excretion	- Hepatic metabolism - Renal & biliary excretion
6- t_{1/2} :	4 hours	4 hours	2 hours

Pharmacodynamics



Types of calcium channels are L, N, T & P.

Mechanism of Action:



Pharmacodynamics

I- Mechanism of Action:

- 1- They **block Voltage-dependent L-type** calcium channels present in Heart, Blood vessels and Smooth muscles.
- 2- **They ↓ Ca^{2+} influx into:**

a-  **Cardiac** muscle → Cardiac inhibition

b-  **Blood vessels** → Arteriolar VD

c- smooth muscle relaxation



2-Pharmacological Action:

A) C. V. S.:

Verapamil & Diltiazem (inhibit Heart > VD):

1- POWERFUL CARDIAC DEPRESSANT:

a- -ve Chronotropic Effect = inhibit SAN = Bradycardia:

- Long Diastolic Perfusion Time for the coronaries.
- Antagonizes Tachycardia induced by Nitrates.

b- -ve Inotropic Effect = decreases Contractility:

- Decreases Cardiac work & Oxygen consumption.
- Contraindicated in Heart Failure.

c- -ve Dromotropic effect = decreases AV Conduction:

VD

- Contraindicated in Heart Block.
- NOT Combined with B-Blockers or Digitalis.

d- **Decreases Automaticity** □ decreases Ectopic Focus Formation

(Class IV Anti-Arrhythmic).

2- Less peripheral V.D. than Nifedipine BUT POTENT

Coronary V.D.



2-Pharmacological Action:

2- Nifedipine (V.D. > Inhibition of Heart):

1- **POWERFUL V.D. (ARTERIAL > Vein in contrast to Nitrates):**

a- **Potent Arterio-Dilator** ↓ TPR ↓ AFTER-LOAD ↓ Cardiac Work &

b- **Weak Veno-dilator** Less ↓ VR ↓ Preload O₂Consumption.

c- **Coronary VD:** BUT VD of SMALL coronaries on the non-ischemic area may steal the blood from the atherosclerosed area → Coronary Steal Phenomenon

d- **Hypotension** :Reflex stimulation of Sympathetic system → Tachycardia

→ Short Diastolic Filling. **Better ADD B-Blocker.**

Better not used ALONE with Nitrates.

2- **Very Weak Myocardial Depressant:**

a- **Does NOT inhibit SAN.** It even causes TACHYCARDIA.

b- **Does NOT inhibit AVN.** Allowed in Heart Block.

c- **Minimal -ve Inotropic** ☐ COP is maintained or may increase ☐ Allowed in HF.

d- It is **NOT an Anti-arrhythmic.**



2-Pharmacological Action:

B) Other Actions of CCB:

- a- Decreases Platelet aggregation mainly in vitro.
- b- Smooth muscle relaxation e.g. Bronchial, Biliary, GIT, Urinary & Uterine.
- c- Endocrine: Verapamil decreases insulin release in large dose.
- d- Skeletal muscle: No effect, they depend on intracellular calcium pool.



Therapeutic Uses of Ca channel blocker

1- Prophylaxis of all types of Angina.

a- Verapamil & Diltiazem:

- Indicated specially in Angina + Cardiac arrhythmia.

b- Nifedipine:

- Indicated specially if angina + Hypertension or Bronchial asthma.

a. Coronary VD → Treat **Variant Angina.**

b. Treat **Effort Angina & Unstable Angina.**

- Decreases Cardiac Work & O₂ consumption
- Powerful arteriolar VD → Decreases TPR → Decreases after-load
- Mild Veno-Dilator → Mild decrease of VR → Mild decrease of Preload.
- Decrease Platelet aggregation.

2- Cardiac Arrhythmias especially Verapamil:

a- IV verapamil is antiarrhythmic supraventricular tachycardia.

b- decreases HR in atrial flutter & fibrillation.



Therapeutic Uses of Ca channel blocker

3- Hypertrophic Obstructive Cardiomyopathy with subaortic stenosis:

Verapamil & Diltiazem □ -ve ino + -ve Chrono □ More filling & arterial VD □
More emptying

4- Hypertension especially Nifedipine □ Arterial VD □
decreases TPR □
decreases Bl.p.

5- P.V.D. especially D.H.P. group.

6- Cerebral spasm in response to subarachnoid hemorrhage: Nimodipine.

7- Migraine headache: Nimodipine & Flunarizine.



Adverse Effects of Ca channel blocker



1- Headache & flush.

2- Heart:

a- Verapamil & Diltiazem □

- -ve Inotropic □ Heart failure.
 - -ve Chronotropic □ Bradycardia.
- with B- Blockers.

NOT combined

- -ve Dromotropic □ Heart Block.

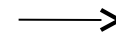
b- Nifedipine □ Tachycardia & may aggravate angina by its steal phenomena.

3- Hypotension.

4- Constipation specially Verapamil.

5- Reversible liver impairment.

6- Ankle edema specially Nifedipine



Drug interactions of CCB.

- a- Verapamil ↓ Renal excretion of Digoxin.
- b- Verapamil + β -Blocker → Severe Cardiac depression.
- c- Nifedipine + Nitrates → Severe Hypotension & Tachycardia





3- B- Blockers

1- All B-Blockers (selective or non-selective) are effective in angina pectoris:

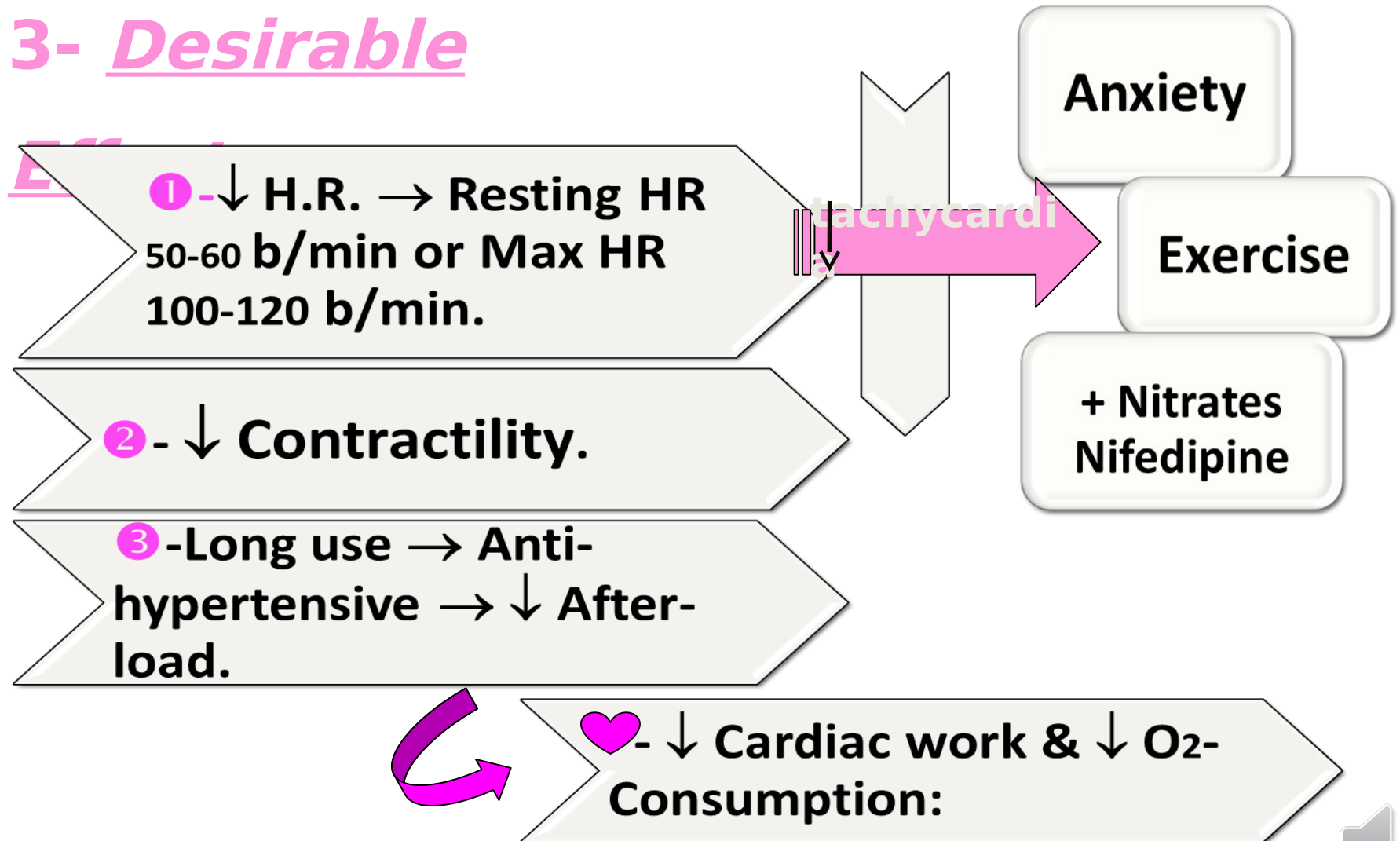
- a- Better use B-Blockers without I.S.A.
- b- Non-selective: Propranolol & Nadolol.
- c- Selective B₁-Blockers e.g. Atenolol, Metoprolol & Bisoprolol.
- d- Vaso-dilator B-Blockers e.g. Carvedilol

2- They do NOT produce coronary V.D. Non-selective B-Blockers may cause V.C. of normal coronaries □ Shift & Redistribution of coronary flow to ischemic area



B-Blockers

3- Desirable



4- Undesirable effects: Bradycardia

→

a- Long diastole → ↑ E.D.V. → ↑ Preload. - ↑ O₂-needs

→ Partially offset the beneficial effects of B-blockers
Block use of nitroglycerine.

 **Useful in
Prophylaxis of
Angina Pectoris:**

**Contraindicated
in Variant
(Prinzmetal)
angina** 

**Stable &
Unstable
angina.**



Drug Group	Decrease Cardiac Work			Coronary VD
	<u>Arterial VD</u> <u>decrease After load</u>	<u>Venodilator</u> <u>decrease Preload</u>	<u>Heart -ve</u> <u>Inotropic & -ve</u> <u>Chronotropic</u> <u>ic</u>	
1- Nitrates		+ + +		+ + +
2- Calcium channel blockers	+ + +		+++ (Verapamil)	+ + +
3- Beta-Blockers			+ + +	

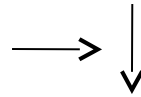


IV- Anti-Platelet Drugs



1- Aspirin in SD :(75–150 mg) →

↓ Platelet TXA-2. Also treats Nitrate-induced headache



2- ADP-Receptors Blockers: Ticlopidine & Clopidogrel.

3- GP IIb/IIIa-Receptors Blockers:
Abciximab & Tirofiban



A) Favorable Anti-Anginal Combinations:

Beta-blocker+ Nitrates:

Nitrates: Coronary VD + Veno-dilator + decrease Preload + reflex stimulation of

Sympathetic system leading to increase Contractility & Tachycardia and Shorten Diastolic Coronary Perfusion Time.

Beta-blocker: decreases cardiac work & O₂-consumption, increases diastolic coronary perfusion time and prevents tachycardia induced by nitrates.

Nitrates+ Verapamil or diltiazem

Nitrates: Coronary VD + Veno-dilator + decrease Preload+ increase HR + decrease diastolic time.

Verapamil : Coronary VD+ Arterio-dilator+ decreases afterload &HR+ increases diastolic time.



Beta-blocker + Nifedipine or amlodipine:

Nifedipine or amlodipine:

- a- Potent Arterio-Dilator decreases TPR & After-load.
- b- Weak Ven o-dilator less decrease in VR & Preload → decrease in Cardiac Work & O₂ Consumption
- c- Hypotension → Reflex stimulation of Sympathetic system → Tachycardia → Short Diastolic Filling

Beta-blockers :

Decreases cardiac work & O₂-consumption, increases Diastolic coronary perfusion time and prevents tachycardia induced by nifedipine or amlodipine.

Beta-blocker + Nitrates + Nifedipine or amlodipine: discussed previously

B) Unfavorable Anti-Anginal Combinations:

- 1- Nitrate + Nifedipine □ Severe Hypotension & Tachycardia.
- 2- B-Blockers + Verapamil □ Severe Cardiac Inhibition.
- 3- Do NOT use 2 drugs of the same class in the same line of treatment.



Other Anti-Anginal Drugs

1- Nicorandil

1-It has a dual mechanism of action:

a- Opens ATP-dependent K⁺-Channel leads to **hyperpolarization**

i. Heart ----- decrease cardiac work

ii. Blood vessels ----- vasodilatation

b- Nitrate-like, Release NO = Nitrodilator.

2-V.D. of Normal Large Epicardial coronaries.

3-Used Orally for treatment of Angina & Heart failure

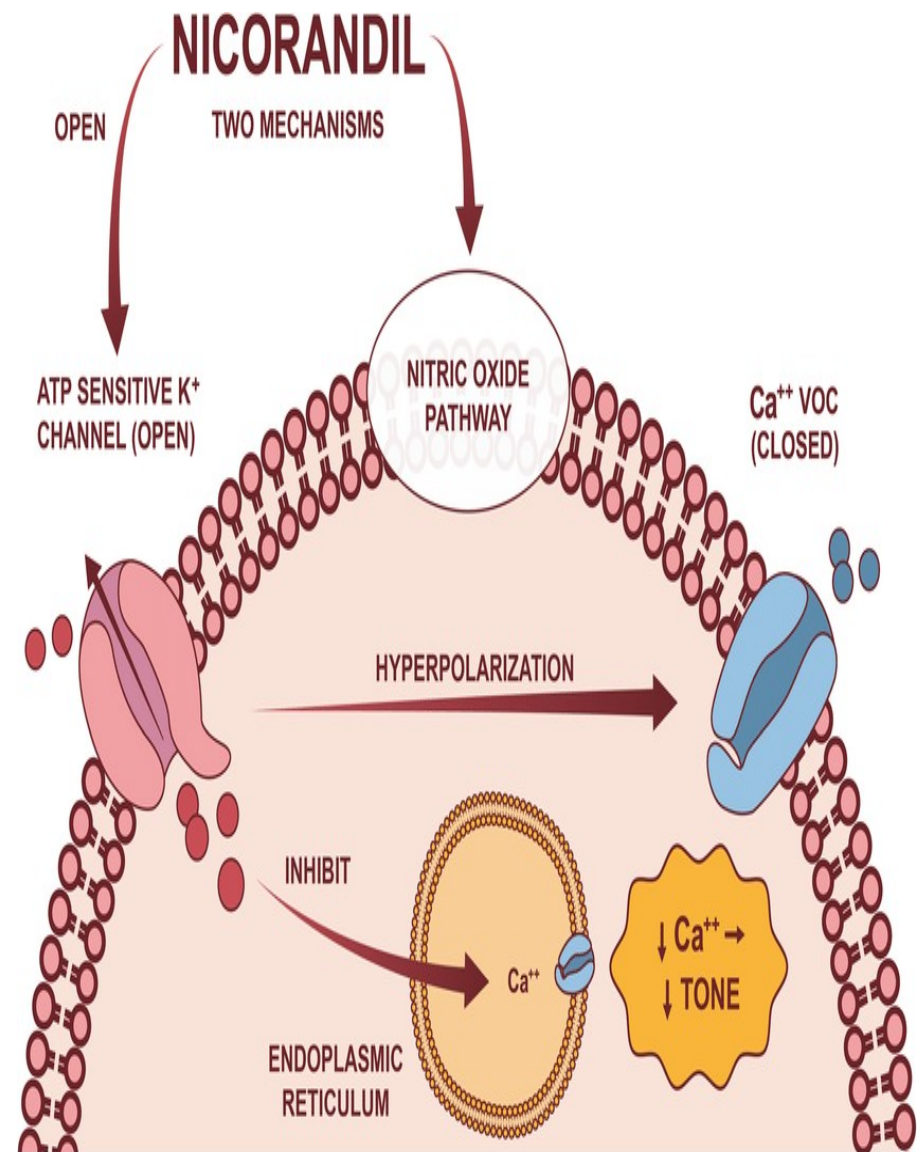
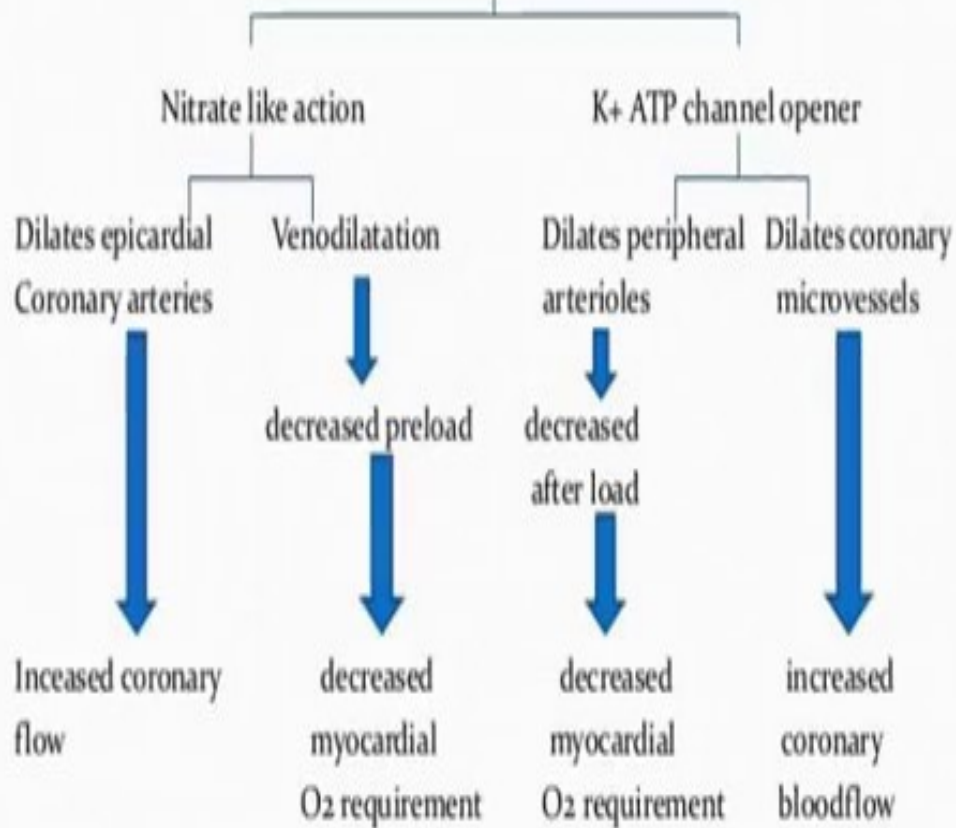
4-The vasodilator action is partly antagonized by K⁺ channel blocker **glibenclamide** (antidiabetic drug)

5- No tolerance BUT may produce Headache.

6- Contraindicated in cardiogenic shock, left ventricular failure, and hypotension.



Nicorandil Dual Action



<https://i.ytimg.com/vi/ZAGzUL8FxFg/hqdefault.jpg>
<https://www.researchgate.net/publication/347857784/figure/fig2/>

Other Anti-Anginal Drugs

2- Trimetazidine

- ①- anti-Ischemic and cytoprotective
- ②- It is metabolic agent which improves myocardial glucose utilization through a reduction in fatty oxidation and a stimulation of glucose oxidation. *The heart favors fatty acids as a substrate for energy production. However, oxidation of fatty acids requires more oxygen per unit of ATP generated than oxidation of carbohydrates.*
- ③- Decreases free radical production.
- ④- Decreases lactate production, and intracellular acidosis.
- ⑤- Decreases intracellular Ca overload.



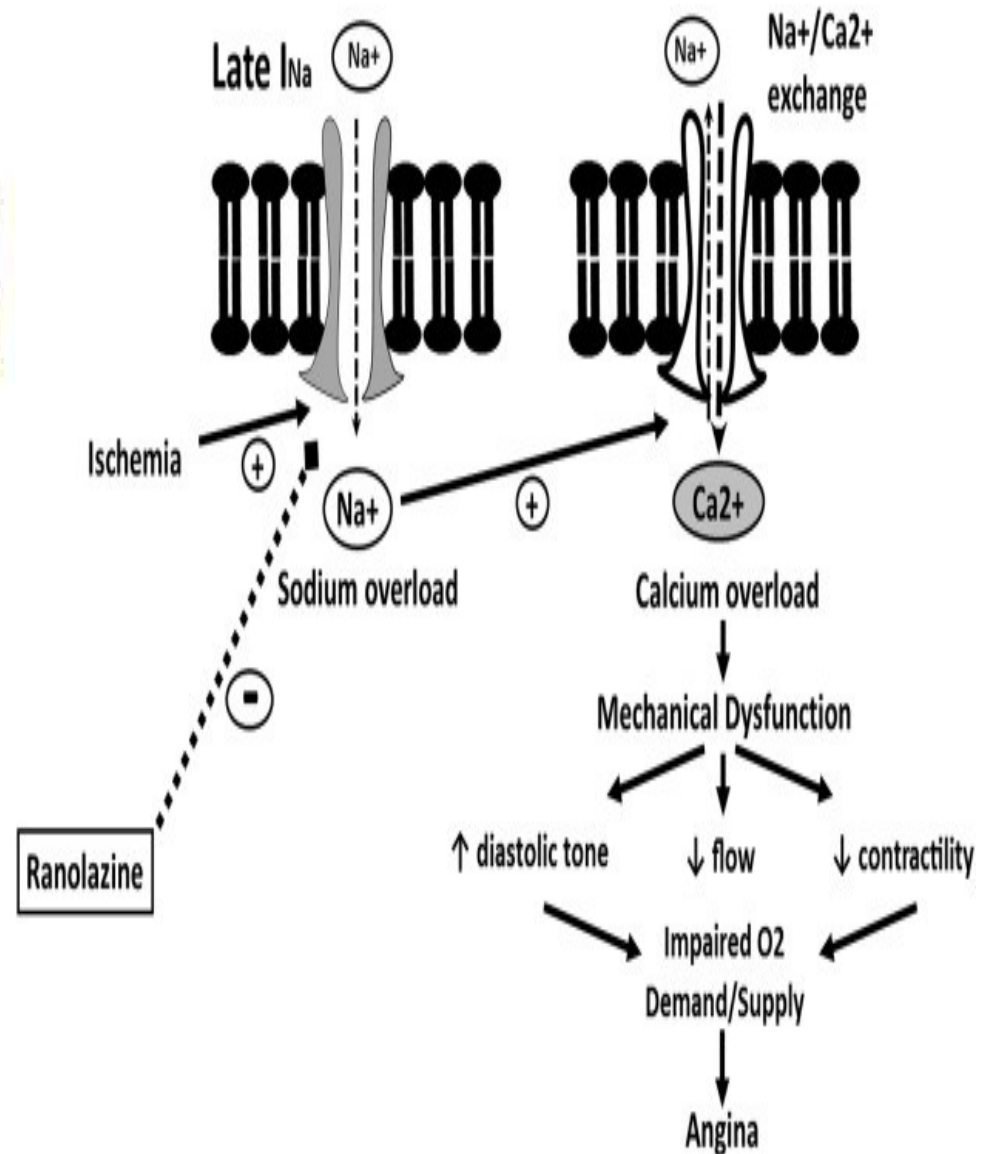
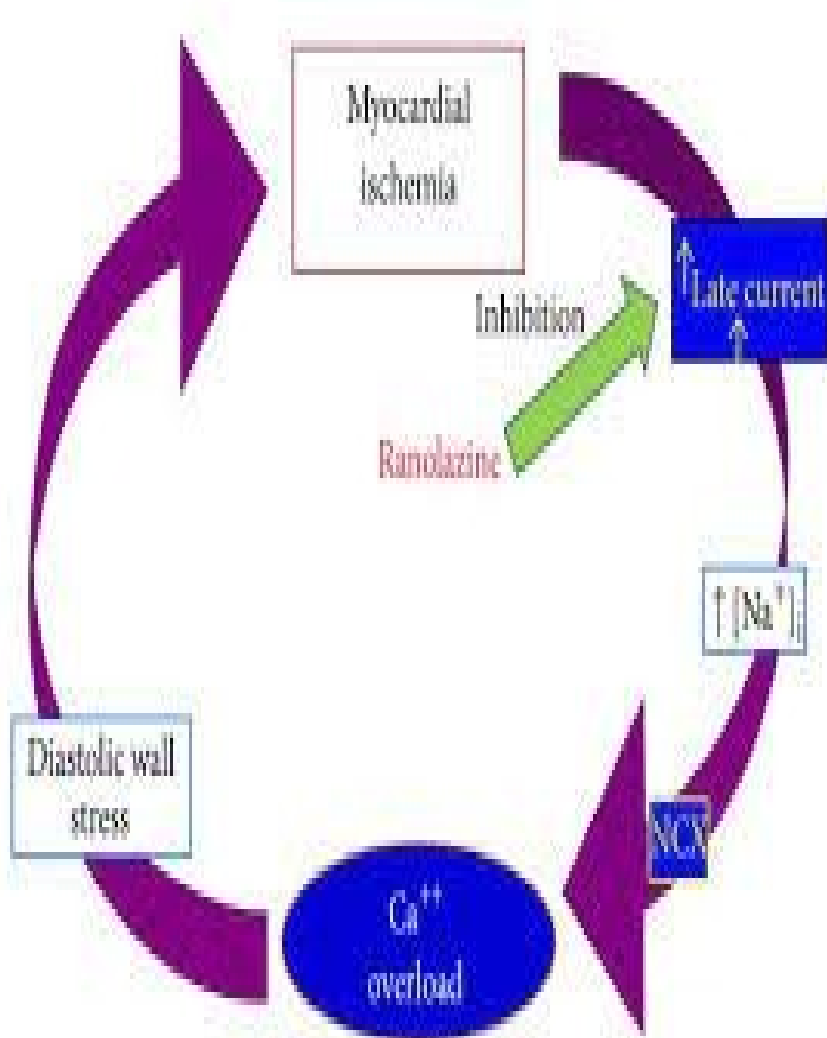
⑤- Used orally in effort angina.

Other Anti-Anginal Drugs

3- Ranolazine

1. Prevents abnormal opening of the late Na⁺ channels in the myocardium which indirectly facilitates Ca²⁺ entry.
2. Reduction in Ca²⁺ overload in the myocardium during ischemia may play an important role in the cardioprotective action of ranolazine leading to:
 - a. decreases myocardial contractility
 - b. decreases Myocardial oxygen demand & increases blood flow to myocardium





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Other Anti-Anginal Drugs

4- Ivabridine

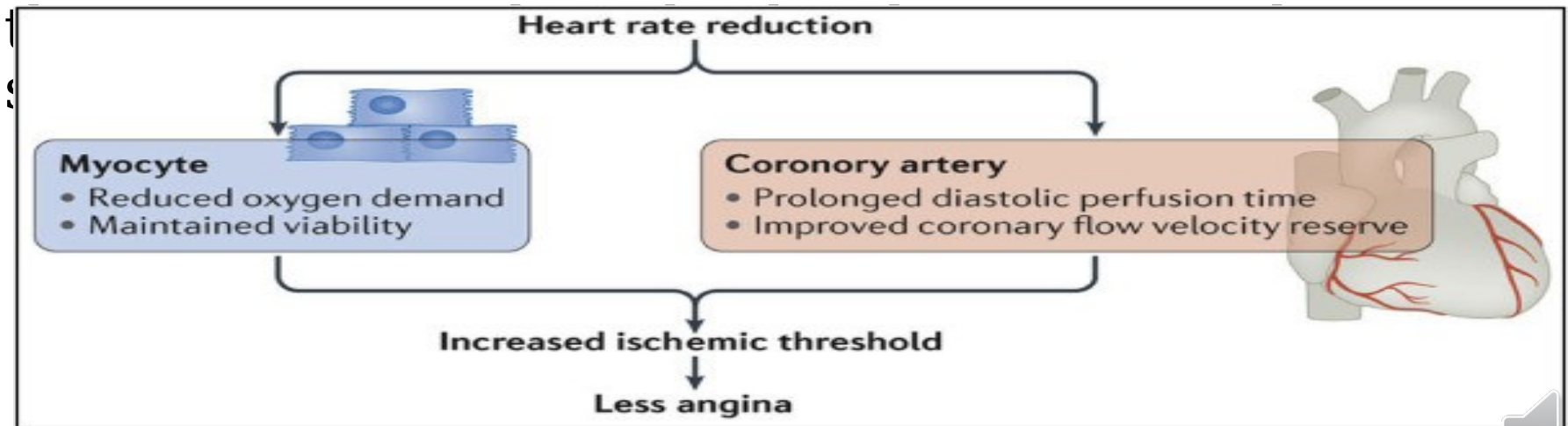
treatment of chronic stable angina pectoris in adult patients:

A- with normal sinus rhythm

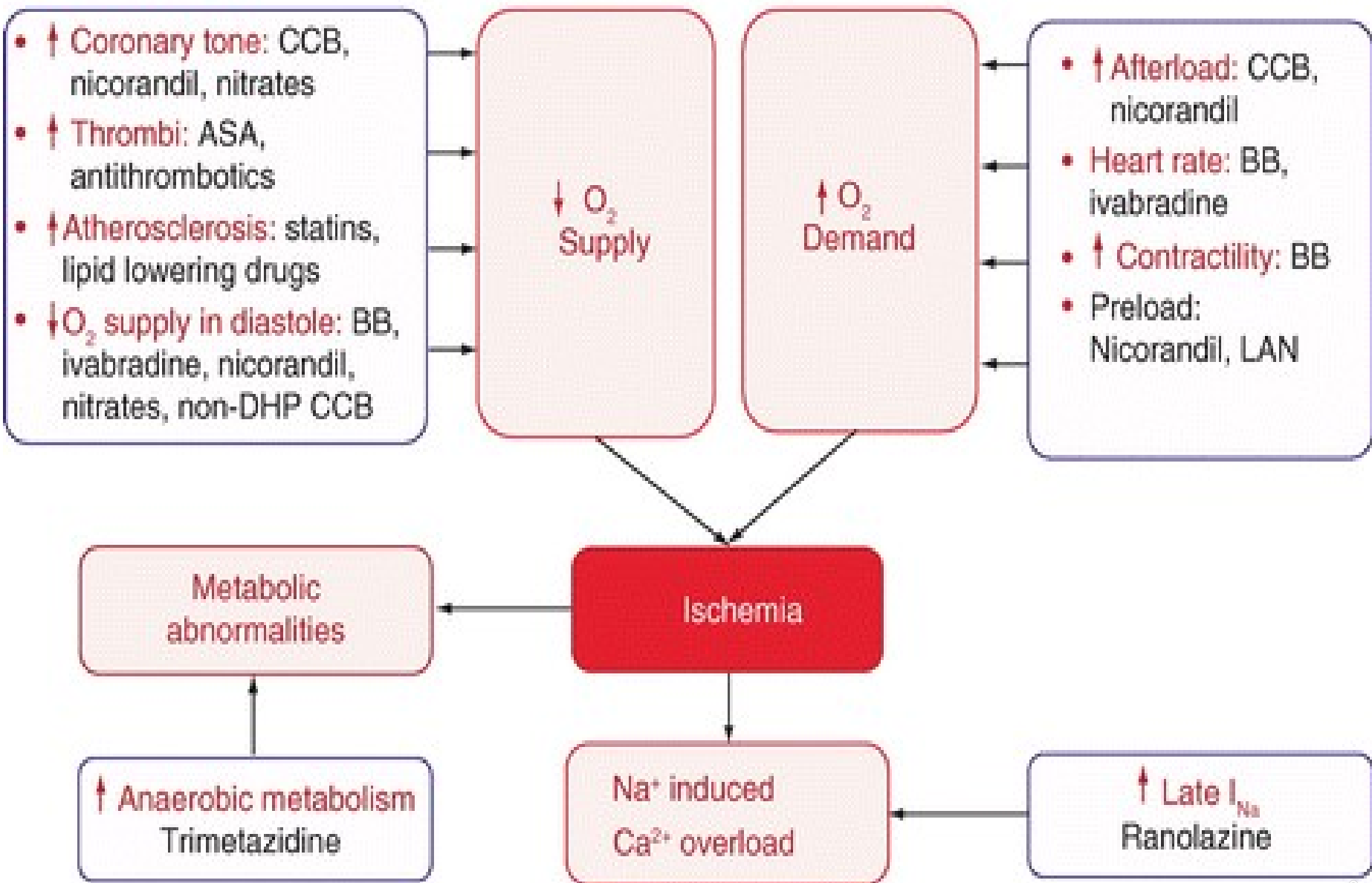
B- with heart rate ≥ 70 / min

Mechanism of action:

Selective and specific inhibition of the cardiac pacemaker funny channels current that controls



Mechanistic targets of antiischemic drugs



1- Mention the mechanism of action of verapamil?

2- Identify the undesirable effects of B blockers as antianginal drugs?



SUGGESTED TEXTBOOKS



1. Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer
2. Neal L. Benowitz, MD. In: Katzung BG (ed.). (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

Cardiopulmonary module



Thank You